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REPORT NO. T5/85

EFFECTS OF ATROPINE UPON COGNITIVE PERFORMANCE AND SUBJECTIVE VARIABLES

U S ARMY RESEARCH INSTITUTE
OF
ENVIRONMENTAL MEDICINE
Natick, Massachusetts

NOVEMBER 1984

UNITED STATES ARMY
MEDICAL RESEARCH & DEVELOPMENT COMMAND

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TECHNICAL REPORT

NO. T5/85

Effects of Atropine Upon Cognitive Performance and Subjective Variables

by

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FOREWORD

In a chemical attack antidotes like atropine may save many lives. Unfortunately, atropine also has undesireable effects (e.g. reduces the body's ability to lose heat) which are exaggerated when the body is not actually challenged by chemical agents. This report investigated if thinking and ability to evaluate verbal and spatial information was impaired by varied doses of atropine.

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ABSTRACT

Seven male soldiers were evaluated with three cognitive tests 125-145 minutes after an i.m. injection of 0, 0.5, 1, or 2 mg of atropine on eight occasions. One dose, 2 mg, was given to all subjects on two occasions; 3 and 4 mg were given to only one and two subjects, respectively. All atropine testing was double-blinded with placebo trials in a hot dry environment (40°C, 20% R.H.). All subjects completed two 50-minute exercise sessions followed by 10 minutes of rest before each testing session.

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1. INTRODUCTION

On the modern battlefield, attack by chemical weapons is a current tactical concern. In this threatening environment, soldiers may inject themselves with antidotes in the absence of actual chemical agents. Such confusion may occur since the bodily sensations produced by high arousal, fear, and danger will be difficult to distinguish from those produced by chemical agents. Since an antidote's adverse effects are much greater when a person has not been exposed to a chemical agent, premature antidote injection in the absence of a chemical threat is a significant problem (5,8, 13). Hence, it is important to identify and predict the effects of antidotes such as atropine on human performance in the absence of chemical warfare agents.

Atropine's effects have been researched extensively since World War II and reviewed recently (6). Many investigations were done in the 1950s, and recent efforts indicate a renewed interest in this area. Investigators have studied the effects of atropine upon ergonomic, physiological, biochemical, visual, subjective, military task, and cognitive indices (e.g. 1, 6-18). Although most experiments have investigated 1 or 2 mg doses of atropine, doses as great as 12 mg have been tested (6,9). With few exceptions, atropine has been given intramuscularly.

Most previous work with atropine has examined its ergonomic and physiological effects. It is well known that 1-2 mg of atropine impairs sweating, increases heart rate, and produces other physiological changes (4, 5, 11, 12, 16). The ability to exercise or do physical work, such as marching or load carriage, is decreased when sweating is impaired since heat storage is increased (11, 12, 16). If the environment and/or the work

demands are severe enough, heat exhaustion and collapse, or even heat stroke, may result.

Atropine also causes visual changes. It dilates the pupil and relaxes the muscles that focus the lens (6). These effects can be demonstrated after 30 minutes with < 2 mg of atropine, and such effects are greatest 2-12 hours after injection (1, 6, 14). It is interesting that the greatest visual effects occur after maximal autonomic effects, e.g. heart rate peaks 60-70 minutes after injection (1, 9, 11, 12). Visual effects such as pupil dilation may persist for 12-24 hours or more (9).

Memory, judgment, computation, pattern recognition and comparison, reaction time, vigilance, and other aspects of information processing have been assessed in cognitive performance studies and are also reviewed by Headley (6). Five tests out of 13 reported in this review were not affected by 2 mg of atropine; i.e., subtraction by successive sevens (13), reading words aloud (13), number recall (13), reaction time to an auditory stimulus (14), and grammatical reasoning (7). The first three of these tests were also investigated with 3 mg of atropine; but no effects were observed (13). Performance did deteriorate after 2 mg on 7 of the 13 tests; i.e., memory for numbers of increasing length (18), reaction time to a visual stimulus (14), number facility (addition) task (7), simple reaction time (7), pursuit rotor (7) and serial responding (7). Visual auditory (choice) reaction appeared to improve with atropine (14); however, this effect may result from a confounding of practice and drug effects. Atropine, i.e. 6-12 mg, 2-9 hours after the initial injection produced impairments on the number facility test in two studies (9, 15) and hallucinations were also noted. One of these was a field study (15) which investigated doses as large as 6 mg while soldiers worked in chemical protective uniforms.

Taken as a whole, these studies of cognitive performance produce varied results after administration of 2 mg atropine; moreover, almost half of the tests reviewed by Headley show no effects. Two recent studies using sophisticated automated measures of visual accomodation, visual search, and target tracking also found no effects for 2 mg of atropine (1, 17).

This study had several objectives: first, to investigate the effects of 0.5, 1, 2, and 4 mg of atropine upon three cognitive performance tests. Second, to determine if repeated administrations of atropine caused cummulative performance effects or performance adaptations. Third, to explore if these doses of atropine produced any hallucinations, dementia, or psychopathology like that observed for larger doses (9,15).

2. METHODS

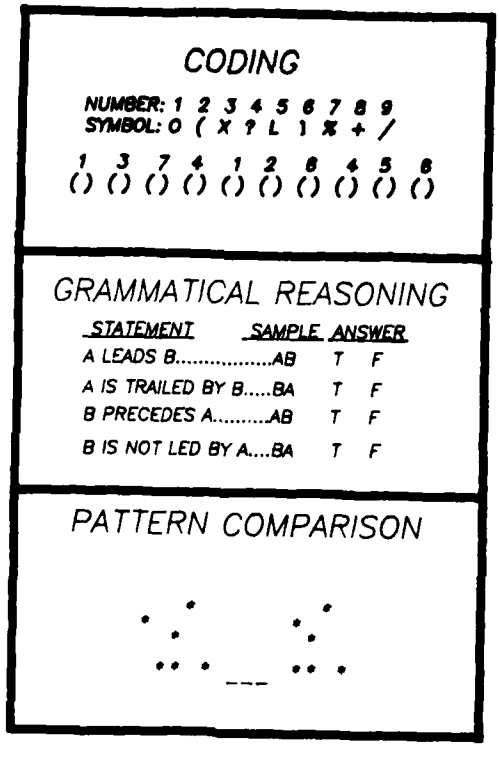
SUBJECTS

Seven healthy male soldiers volunteered for this study. Physical characteristics (mean ± SD) of the subjects were: Age, 24.0 ± 2.9 years; height, 173.9 ± 12.0 cm; weight, 75.7 ± 3.1 kg.

ASSESSMENT INSTRUMENTS

Cognitive performance was evaluated with the Coding, Pattern Comparison, and Grammatical Reasoning Tests. Sample items are shown in Fig 1; these tests were adapted from those described by Carter and Sbsia (2). Dementia was tested with a plain, white card and selected cards from the Rorschach Inkblot Test and personality factors were evaluated with the Minnesota Multiphastic Personality Inventory (MMPI).

Figure 1. Sample items from the Coding, Grammatical Reasoning, and Pattern Comparison Tests used in the present study. A subject codes a unique symbol for a given number described in a legend when completing the Coding Test. With the Grammatical Reasoning Test a subject decides whether the relative positions of two letters (in a sample) are described correctly by a statement. A subject indicates if two spatial patterns in a problem are the same or different on the Pattern Comparison Test. All tests are timed, have several alternate forms (equivalent problems for repeated testing), and are scored for both speed and accuracy (problems attempted per minute and errors per minute).



PROCEDURES

In the first four days of the study, the subjects were heat acclimatized and trained on the cognitive test battery three times daily (3 minutes per

test per administration). On the fifth day, double-blind drug testing procedures were begun. Subjects received injections of normal saline, i.e. placebo, on study days 5, 10, and 16. Atropine (0.5, 1, 2, 2 mg replicate, and varied doses) was injected on study days 6, 8, 12, 14 and 18, respectively. On day 14, after subjects had completed the 2 mg replication, informed consent for higher doses of atropine was sought. Subjects rested and were not tested or involved in the study on days 7, 9, 11, 13, 15, and 17.

Each study day, subjects were equipped with temperature and heart monitoring equipment, injected with atropine or placebo, exercised in a hot dry environment (40°C. 20% R.H.), and evaluated with the Rorschach cards and cognitive performance tests. The psychological testing was done approximately 125-145 minutes after atropine injection and was preceded by two 50-minute bouts of treadmill exercise (12). Each cognitive test and the Rorschach cards were evaluated once daily--the MMPI was only administered before and after the study. Core temperatures were recorded before and after cognitive testing.

Cognitive performance data were analyzed for number of problems attempted and number of problems wrong so rate-accuracy tradeoffs could be identified. Control performance, on days when the placebo was given, was analyzed for trends, i.e., typically improvements due to practice. Performance data (problems attempted and problems wrong) were adjusted, for days when atropine was given, to remove such trends so all drug effects could be compared against the day 5 control values.

Repeated Measures Analysis of Variance was calculated with programs from BMDP (3). Limited multiple comparisons (0.5, 1, 2, and 2 mg replication versus placebo) were performed using Tukey's critical difference test. All significance levels were $p<0.10$ (2-tailed).

3. RESULTS

All subjects completed the study. Three subjects consented to testing at higher doses on day 18; one subject received 3 mg and two subjects received 4 mg of atropine. Two of the remaining subjects received 0.5 mg of atropine; two, received 2 mg. The 2 mg and higher doses of atropine did create some heat storage problems and not all subjects completed the entire 100 minutes of exercise (12).

The number of problems attempted per minute on the Coding, Grammatical Reasoning, and Pattern Comparison Tests is shown in Fig. 2 for varied doses of atropine. The bracket below each function (2 mg dose) shows test performance when 2 mg of atropine was administered the second time. Coding values are one third their actual values since they were transformed to be displayed with the other data. As mentioned, the data for 3 and 4 mg of atropine are based upon only one and two subjects; respectively.

Figure 2. Cognitive test performance (number of problems attempted/min) on the Coding, Grammatical Reasoning, and Pattern Comparison Tests for 0.5, 1, 2, 3, and 4 mg of atropine. All data are from 7 subjects except that for 3 and 4 mg of atropine; data for these larger doses are from 1 and 2 subjects, respectively. The bracket below each function at the 2 mg dose shows performance on each test during the 2 mg replication dose. The Coding data were transformed to one third their actual values so they could be graphed on this Figure.

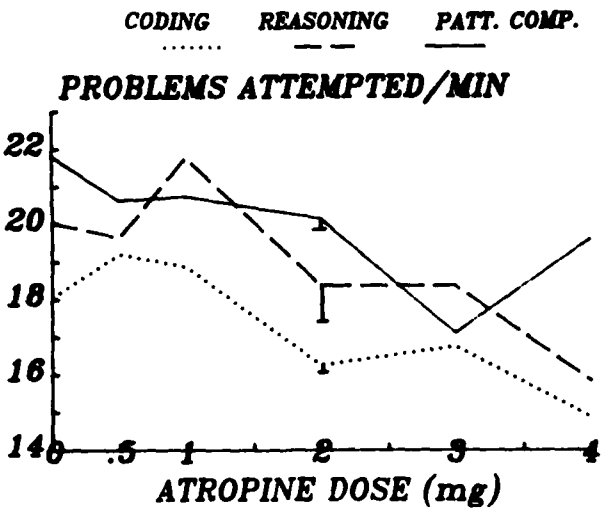


Table I. Performance data (problems attempted per minute and problems wrong per minute) for the Coding, Grammatical Reasoning and Pattern Comparison Tests for 0, 0.5, 1, and 2 mg of atropine and the 2 mg replicate. Also shown are the significance levels for the 1-Way Analysis of Variance and Tukey's Honestly Significant Difference statistical tests.

Cognitive Performance Measure

	Number Problems Attempted/Minute						Number Problems Wrong/Minute					
Cognitive Test	ANOVA: Atropine Effect?	Mg Atropine 0	.5	1	2	2 (rep)	ANOVA: Atropine Effect?	Mg Atropine 0	.5	1	2	2 (rep)
Coding	Yes***	54.2	57.6	56.6	48.7	47.9+	No	0	0.5	0.14	0	0
Grammatical Reasoning	Yes***	20.0	19.7	21.8	18.4	17.5+	No	1.62	1.97	1.46	2.06	1.41
Pattern Comparison	No	21.8	20.6	20.7	20.1	19.9	Yes***	1.38	2.76**	1.06	1.14	0.75

NOTE: + = $p \leq 0.10$
** = $p \leq 0.01$
*** = $p \leq 0.001$

The number of Coding problems that were attempted increased slightly for the 0.5 and 1 mg doses. Although Coding errors were infrequent during this study, all Coding errors occurred during the 0.5 and 1 mg doses (See Table 1). The number of Coding problems that were attempted decreased 10 and 11.5% from control values for the 2 mg and 2 mg replication doses, respectively. Coding performance was significantly different than control ($p<0.10$) during the replication. With the 3 and 4 mg doses, even fewer Coding problems were attempted.

Grammatical Reasoning performance was very similar to Coding (See Fig. 1). The number of problems attempted for 0.5 mg of atropine was similar to baseline; with 1 mg of atropine more problems were attempted. The number of Grammatical Reasoning problems attempted decreased 8.5 and 12.5% from baseline for the 2 mg dose and its replication. Grammatical Reasoning performance, like Coding Performance, was also significantly different than control during the replication ($p<0.10$). With 3 and 4 mg of atropine even fewer Grammatical Reasoning problems were attempted. Although the number of Grammatical Reasoning errors were never significantly different from control, the error rates were greatest for 0.5 and 2 mg of atropine.

The number of Pattern Comparison problems attempted shows a gradual decrease from baseline with increasing doses of atropine. Number of problems attempted decreased 8 and 9% for the 2 mg and replication doses, respectively; however, such changes were not statistically significant. The first time atropine was administered (0.5 mg) errors increased ($p<0.01$) by 100%.

Core temperatures of 38.3°C during cognitive testing were elevated approximately 0.8°C above control (placebo) values during the 2 mg dose. Only small increases in body temperature of 0.05 and 0.1°C, were observed for 0.5 and 1 mg of atropine.

Responses to selected Rorschach cards and the blank card were not suggestive of hallucinations or toxic effects for any of the doses in this study. The test examiner noted, however, that many subjects gave very concrete descriptions of the ink blots, i.e. descriptions without abstraction, symbolism, or synthesis. Before and after MMPI scores yielded no significant changes.

4. DISCUSSION

This study evaluated cognitive performance with the Coding, Grammatical Reasoning, and Pattern Comparison Tests as a function of 0.5, 1, 2, 3, and 4 mg of atropine. The two largest doses were evaluated with only one and two subjects; respectively. Cognitive performance impairments were demonstrated on all tests with atropine. Impairments were also observed the first time atropine (0.5 mg) was given. Cognitive performance on the Coding and Grammatical Reasoning Tests was impaired with 2 mg of atropine (replication). Fewer problems on each test were attempted. Increased errors resulted on the Pattern Comparison Test after only 0.5 mg of atropine. These data contrast with some previous studies that did not find cognitive performance changes on one or more performance tests with 2 mg atropine (1,7,13,17). Our Grammatical Reasoning impairments during the 2 mg replication also contrast with a prior study (7) that did not find effects with this test. Also, to the best of our knowledge, this is the first time that the Coding and Pattern Comparison tests have been used in an atropine study.

The 2 mg replication provided an opportunity to determine whether atropine had residual (cumulative) performance effects with repeated dosing. When the initial 2 mg data and the 2 mg replication data were compared, test

results did not differ significantly. These data suggest that there were no cumulative effects from atropine.

During the 2 mg replication, Coding and Grammatical Reasoning performances (problems attempted per minute) were significantly decreased from control performance levels; whereas, performance during the first 2 mg atropine challenge was not. Furthermore, impairments during the replication resulted in 2% fewer coding problems attempted (no change in error rate) than with the same atropine dose 48 hours earlier. During the 2 mg replication, 5% fewer Grammatical Reasoning problems were attempted than during the previous 2 mg dose; however, 32% fewer errors resulted at the slower rate. Hence, when fewer Grammatical Reasoning problems were attempted, fewer errors resulted. Similar trends for problems attempted and errors were observed for Pattern Comparison. Such tradeoffs between problems attempted and errors have been commonly observed in other performance studies (19). Since heart rates were lower during the 2 mg replication (12), subjects may have been more relaxed and this may have contributed to the problem solving strategy observed during the replication.

In the present study the subjects' responses to the blank Rorschach card did not suggest toxicity or hallucinations. Even when one subject received 3 mg and two subjects received 4 mg of atropine, verbal responses were not indicative of toxicity or hallucinations. Hallucinations were reported in other studies after 3 mg in 4 out of 20 subjects (13) and after 6 mg (9,15). Ten to 12 mg of atropine is the predicted effective dose to produce hallucinations in 50% of normal humans (9). Similar MMPI scores, before and after the study, indicate that the atropine doses and the stressors in the present study did not induce or precipitate any psychopathology.

The trends in this study are probably underestimates of the actual effects of atropine. The subject sample size and the atropine dose ordering are probably the two greatest implicating factors. The only trends that were statistically different from control were the decreased number of problems attempted for Coding ($P \leq 0.10$) and Grammatical Reasoning ($P \leq 0.10$) during the 2 mg replication and the increased problems wrong ($p < 0.01$) the first time atropine (0.5 mg) was given.

In the present double-blind study, the drug doses were given in increasing magnitude to minimize possible adverse subject reactions. Hence, before anyone received 2 mg of atropine they had previously experienced 0.5 and 1 mg. Subjects receiving 3 or 4 mg had previously experienced 0.5, 1, 2, and the 2 mg replication before the larger dose. Such sequencing of the drug doses, rather than a random or systematically-varied sequence, would provide maximal opportunities for subjects to behaviorally compensate for some of the effects of atropine before they experienced the larger doses. This is supported by the increased errors that were observed on the Pattern Comparison Test when the first dose (0.5 mg) was given. Likewise, errors on the Grammatical Reasoning Test for 0.5 mg, although not statistically significant, were among the greatest observed for this test. Also, the only errors observed on the Coding Test were for the 0.5 and 1 mg atropine doses. We suspect these impairments resulted because atropine produced visual and/or bodily changes that the subjects had not experienced during the placebo trials. The fact that the higher doses did not result in increased errors suggests that some initially disruptive bodily changes e.g. blurred vision, sensitivity to light, "stirred up" feeling, can be compensated for (within limits) and tolerated as one gains familiarity and experience with them.

The present study with seven subjects reduced the chances that observed effects would be significant since the statistical confidence or certainty of an experimental effect is determined by the effect magnitude, the measurement variability, and the number of subjects studied. Statistically, 12 subjects or more is desireable in a behavioral experiment unless the effect is great and/or variability is small. In fact, previous studies (7,9,14-16,18) demonstrating performance effects for 2 mg of atropine used a minimum of 10 subjects; whereas, studies reporting no performance changes used a minimum of 6 subjects. The fact that our findings were statistically significant, i.e., $p<0.10$, with small changes in the magnitude of the effect (see Fig. 2) suggests that with more subjects our findings would also have been significant at conventional probability levels.

Given the cognitive performance impairments observed in this and other studies it is of practical importance to establish how atropine causes such performance changes. Three possibilities are evident: first, increased body temperatures resulting from atropine's disruption of sweating; second, visual changes caused by atropine; and third, central nervous system effects. Although data from the present study do not answer this question, atropine's direct effects upon the central nervous system are the most likely possibility (4,9,13). For example, increased body temperature does not seem responsible since most previous studies that show cognitive performance changes have studied sedentary subjects without exercise or increased body temperatures (7,14,18). A field study (15) and the present experiment are the only studies of which we are aware that have evaluated cognitive performance following increased heat storage. We observed increased body temperatures during the 2 mg and higher doses but we do not think that they produced the performance changes. Also we doubt that visual

change are the main cause of the performance changes since pupil dilation and changes in accomodation, are observed earlier than the cognitive performance changes (1,9,15). Furthermore, in one study (9) the greatest effects on the Number Facility Test (addition) occurred before the eyes (pupils) were maximally dilated. Also, task analysis of cognitive tests in prior atropine studies shows that some tests involved no or minimal visual acuity, e.g., digit span, simple reaction time, and visual reaction time, yet performance impairments were found (7,14,18). Finally, a recent study using sophisticated measures of target detection and visual processing did not find performance changes with atropine (1).

We suspect that the cognitive performance changes observed with atropine are due to its direct effects upon the central nervous system. Atropine initially stimulates but then depresses the central nervous system (13). This hypothesis seems to account best for atropine's delayed effects upon cognitive performance which occur after blood levels and heart rate have reached their maximum (7,9,15). For example, Ketchum et. al (9) showed dose and time response curves for cognitive performance with maximal effects observed from 2-9 hours. Their observations of profound changes in emotion, perception, speech coherency, and reality testing following doses of atropine greater than 2 mg also suggest atropine's effects are more generalized than just upon vision or thermoregulation.

5. CONCLUSIONS

1. Coding and Grammatical Reasoning performances were impaired after 2 mg of atropine. Performance changes were manifested as fewer problems attempted per minute on each task as subjects took longer to complete problems.

2. Pattern Comparison errors increased markedly the first time atropine was given. The absence of such changes with larger, subsequent atropine doses suggests some disruptive visual and/or bodily changes were tolerated as subjects gained more experience with them. Some operational performance impairments (after injection with atropine and in the absence of chemical agent) can probably be minimized by prior experience with atropine during training.

3. The similarity of cognitive performance on each test for the 2 mg dose and its replication suggests there were no cummulative atropine effects.

4. The demonstrated cognitive performance impairments on our highly practiced and overlearned tests after 2 mg of atropine suggest some military tasks will be impaired when soldiers inject themselves with atropine, especially in the absence of a chemical attack. Tasks requiring rapid performance with few errors will be most vulnerable.

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7. ADDENDUM

An eighth subject volunteered and participated in the entire study. This subject's data were not included in our analyses since he never received a dose of atropine >0.5 mg.

Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of Volunteers in Research.

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